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CERA

Antianemic Agent
Erythropoietin Receptor Agonist

R-744
Ro-50-3821

Continuous erythropoietin receptor activator

EN: 316296

Abstract

CERA (continuous erythropoietin receptor activator) is an erythropoietin (EPO)-stimulating agent developed for the treatment of anemia related to chronic kidney disease (CKD) and cancer. It is a third-generation pegylated recombinant human EPO with a longer elimination half-life than previous molecules (epoetin and darbepoetin alfa), and with reduced immunogenicity. Preclinical and clinical studies indicate that CERA may be as effective as the first- and second-generation EPOs in treating anemia, but require less frequent dosing. It is undergoing regulatory review for anemia associated with CKD and phase II trials are under way in cancer patients with chemotherapy-induced anemia.

Background

Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidneys that circulates through the bloodstream to stimulate red blood cell production (erythropoiesis) in response to a drop in oxygen levels in the blood. Deficiencies in red blood cells (and consequently hemoglobin levels) result in a reduction in the oxygen supply to tissues, causing hypoxia and anemia. The symptoms of anemia include fatigue, shortness of breath, increased heart rate and palpitations, poor concentration, loss of cognitive function and a depressed immune system. Anemia is also associated with chronic kidney disease (CKD), as well as with reduced survival rates in cancer patients receiving chemotherapy (1-4).

Recombinant human EPO (epoetin; marketed as Epogen® by Amgen) has been used since the 1980s to manage anemia caused by CKD. In addition to managing the symptoms of anemia, there is evidence that it slows the progress of kidney disease. It was also subsequently approved for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies. There are two forms of recombinant human EPO –epoetin alfa and beta–, with minor qualitative differences in the composition of the *N*- and *O*-linked glycans, and most studies have shown that they are biologically equivalent and equivalent to natural human EPO. Epogen® (epoetin alfa) has a half-life of 6-8 h and is administered 2-3 times a week either s.c. or i.v. In 2001, a second-generation recombinant human EPO, darbepoetin alfa (Aranesp®) was introduced as a once-weekly injectable formulation (3, 5-7). Darbepoetin alfa has two extra *N*-linked oligosaccharide chains that reduce interactions with the enzymes involved in drug clearance, providing an improved pharmacokinetic profile ($t_{1/2}$ = 18-24 h).

CERA (continuous erythropoietin receptor activator), a new recombinant human EPO conjugated with a large methoxy-polyethylene glycol (PEG) polymer chain, is more potent than epoetin in stimulating erythropoiesis and has an improved pharmacokinetic profile compared to both epoetin and darbepoetin alfa, with a half-life of 135 h and an expected dosing interval of once every 2-4 weeks (8). CERA is undergoing regulatory review in the U.S. and the E.U. (9, 10) as an injectable formulation incorporating Nektar Therapeutics' PEGylation technology for anemia associated with CKD, and phase II trials are under way in cancer patients with chemotherapy-induced anemia.

Preclinical Pharmacology

The *in vitro* activity of CERA was somewhat less than that of epoetin in stimulating the proliferation of UT-7 human myeloid leukemia cells which express the EPO receptor, reflecting different binding characteristics (11-13). However, *in vivo* in various animal species, it exerted greater erythropoietic activity than epoetin following single or multiple s.c. or i.v. doses. A single dose of CERA (20 μg/kg s.c.) in mice increased the reticulocyte count by 13% compared to 7.8% for the same dose of epoetin beta, and the effect lasted for 3 days longer. At 2.5 μg/kg i.v. or s.c., single doses of CERA produced a greater and longer lasting response than multiple-dose epoetin, and CERA (administered once a week at 1.25 μg/kg s.c., or once every 2 weeks at 1.25 or 5 μg/kg s.c.) maintained

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the same level of reticulocyte count as epoetin beta dosed 3 times a week (1.25 μg/kg s.c.) (11-15).

In a nephrectomized rat model of anemia-associated CKD, administration of CERA (2.5 μg/kg s.c.) once a week for 4 weeks increased hemoglobin (Hb) levels by 7 g/dl above baseline, compared to 3 g/dl for epoetin (2.5 μg/kg s.c. 3 times a week) and 1 g/dl for vehicle-treated controls. At a lower dose of CERA (0.75 μg/kg s.c.) administered once a week for 12 weeks, Hb levels increased by 6 g/dl, whereas they declined by 2 g/dl with epoetin on this dose and schedule (14, 16). No animals developed antibodies following CERA treatment, whereas 69% of animals given epoetin showed antibody formation (16).

Pharmacokinetics and Metabolism

In vitro studies indicated that CERA is not removed during hemodialysis or hemofiltration (17, 18).

The compound has an excellent pharmacokinetic profile in animals, with a much lower systemic clearance and a longer terminal half-life than epoetin. CERA showed a median serum half-life in dogs of 49.0 h *vs.* 6.4 h for epoetin following i.v. administration (11-15). In healthy volunteers entered in two randomized, placebo-controlled studies and treated with i.v. CERA (0.4-3.2 μg/kg) or s.c. CERA (0.1-3.2 μg/kg), the half-lives were 70-122 and 102-216 h, respectively (11).

In an open-label, randomized study in healthy volunteers (n=42), the site of administration of s.c. CERA was determined to have no clinically relevant effect on its pharmacokinetics; CERA (3.0 μg/kg s.c.) was injected into the abdomen, arm or thigh, with a 7-week washout period between each injection. The AUC was similar for all sites and peak plasma levels (14.2-16.5 ng/ml) were reached at a median of 96 h at all sites; the mean $t_{1/2}$ was 160-164 h for all sites (19, 20).

To test the effect of repeated dosing on the pharmacokinetic profile of CERA in healthy volunteers, subjects were randomized to receive either i.v. CERA (0.4-3.2 μg/kg) or placebo once every 3 weeks for 9 weeks (n=61), or s.c. CERA (0.4-3.2 μg/kg) or placebo once every 2 weeks for 8 weeks (n=48) in two separate studies. The mean half-lives were 133 and 137 h, respectively, for i.v. and s.c. CERA. No accumulation was seen in either study and the pharmacokinetic profile was unaffected by repeated dosing (21-23).

An open-label, crossover trial evaluated the bioavailability, pharmacokinetics and pharmacodynamics of two different formulations of CERA, both administered as a single s.c. dose of 3.2 μg/kg, in 36 healthy volunteers. The results showed no significant differences between formulations and confirmed the low clearance, small volume of distribution and long elimination half-life (141-169 h) of CERA (24).

Clinical Studies

Studies in healthy volunteers demonstrated that CERA (i.v. or s.c.) produced a prolonged, dose-dependent erythropoietic effect, reticulocyte counts peaking at 334% and 262% of baseline, respectively, 7-10 days after administration of 3.2 μg/kg i.v. and s.c., with the levels returning to baseline after 20 days (21, 22, 24-27). Dose-dependent increases in soluble transferrin receptor levels and decreases in serum ferritin and iron levels were also seen (25-27).

Sixteen previously untreated patients with anemia (Hb < 12 g/dl) related to CKD and receiving dialysis were enrolled in an open-label, randomized, multicenter, crossover study to receive single doses of i.v. CERA (0.4 μg/kg) or s.c. CERA (0.8 μg/kg). Reticulocyte counts peaked at day 8 for both routes of administration (73% and 92%, respectively, above baseline for i.v. and s.c. CERA). Treatment was well tolerated, gastrointestinal adverse events being the most frequent (28).

In two multicenter phase II studies, epoetin-naïve patients with CKD and low Hb levels (8-11 g/dl) were randomized to one of three doses of CERA (0.15, 0.3 or 0.6 μg/kg/week s.c.) given once a week, once every 2 weeks or once every 3 weeks. In one study, 61 patients were followed for 12 weeks. The primary efficacy variable was the rate of increase in Hb over 6 weeks in the intent-to-treat population. Mean increases were 0.84, 1.15 and 1.11 g/dl for the respective doses over the first 6 weeks and 1.15, 2.50 and 2.35 g/dl, respectively, during the entire study. Response was not related with dosing frequency but response/response rate and time to response were related to dose. The only adverse event attributed to CERA was 1 case of pruritic rash (29). A significant relationship was observed between the change in Hb and median CERA serum levels and a dose-dependent reticulocyte response was also seen (30). Another study was conducted in 65 patients who received the same doses and schedules as above for a total of 18 weeks. Similar results were obtained and CERA was well tolerated, infections and gastrointestinal disturbances being the most frequent adverse events; no antibodies were detected (31-34). Fifty-one patients continued treatment during a 54-week extension and Hb levels were maintained (11.3-11.9 g/dl) to a similar extent on all the dosing schedules (33).

In two multicenter, dose-finding phase II studies, CKD patients who were already receiving dialysis and epoetin therapy (80-250 IU/kg/week 3 times a week) for anemia were switched to CERA (i.v. or s.c.) and the effect of the switch on blood Hb levels was monitored. In the first study, after an initial 2-week run-in period, patients (n=91) were randomized to one of three doses of i.v. CERA (0.25, 0.4 and 0.6 μg/150 IU epoetin) either once a week or once every 2 weeks for 19 weeks. A significant dose-response was observed, with a mean change in Hb levels of –0.8, –0.16 and +0.37 g/dl for the respective doses. The treatment group with the highest percentage of patients (77%) maintaining their Hb levels within 1.5 g/dl of baseline was the group receiving 0.6 μg/150 IU conversion factor once every 2 weeks. The treatment was well tolerated (35). In a 12-month extension to this study (n=53), Hb levels were maintained between 11.03 and

12.02 g/dl on both schedules (36). In the second study, after a 2-week run-in period, patients (n=137) were randomized to one of three doses of s.c. CERA given once a week or once every 3 weeks for 19 weeks, or once every 4 weeks for 21 weeks. A significant dose-response was observed, with a mean change in Hb levels of –0.63, –0.1 and +0.48 g/dl, respectively, on the three doses, irrespective of dosing frequency (37). In a 12-month extension to this study (n=61), Hb levels were maintained between 10.65 and 11.64 g/dl for all administration cohorts (38).

A total of 109 patients from both the above studies entered a 12-month extension period. The beneficial effects on Hb were found to be independent of gender, age, race or diabetic status, as well as iron status and inflammation (39, 40). Moreover, CERA was shown to adequately control blood pressure in these patients (41). The most frequent adverse events were hypotension, muscle cramps, hypertension, headache and nasopharyngitis, and the most common serious adverse events were hypotension, myocardial infarction, cellulitis and pancreatitis (42).

Several phase II and III trials are ongoing or have been completed to assess the efficacy and safety of CERA for the treatment of anemia in patients with chronic kidney disease (43-50). The product has been submitted for regulatory review in the U.S. and the E.U. for this indication (9, 10).

Sixty-four patients with multiple myeloma and anemia related to chemotherapy were enrolled in an open-label, multicenter, two-stage phase II study and randomized to CERA (1, 2, 3.5, 4.2, 5.0, 6.5 and 8 μg/kg s.c.) once every 3 weeks for 6 weeks, followed by an optional extension period of 12 weeks. Dose-dependent increases in Hb, the primary efficacy variable, were seen after 6 weeks of CERA treatment up to the 4.2 μg/kg dose, followed by an apparent plateau of Hb levels at higher doses. Doses of 3.5-8.0 μg/kg provided mean Hb increases of 1.6-2.3 g/dl and at least 50% of patients showed an increase of at least 2 g/dl during the first stage of the study. Hemoglobin levels were maintained or improved with further treatment and up to 90% of patients had an increase of 2 g/dl by 18 weeks. Adverse events included several cases of hypertension and 1 case of pyrexia (51-54).

A phase II study is ongoing and another has been completed in patients with cancer-related anemia receiving chemotherapy (55, 56).

Sources

F. Hoffmann-La Roche, Ltd. (CH); Nektar Therapeutics is providing its PEGylation technology.

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